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# Expanded Phenotype of Cranioectodermal Dysplasia (Sensenbrenner Syndrome)

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**Cranioectodermal dysplasia (CED) is an autosomal recessive condition characterized by defects of ectoderm-derived structures and characteristic bone anomalies. We report on a 27-month-old Caucasian girl with CED, pre- and postnatal growth retardation, microcephaly, hypoplasia of the posterior corpus callosum, photophobia, and aberrant calcium homeostasis. Since new traits were encountered, we reviewed all reported patients and one unpublished case and compared the frequency rates of the individual manifestations. The findings present in all patients are dolichocephaly and rhizomelia. Ectodermal dysplasia manifestations are variable. Short thorax and heart defect are inconsistent. Previously unreported anomalies include growth deficiency, delayed psychomotor development, microcephaly, photophobia, and abnormal calcium homeostasis.**

**These clinical manifestations may facilitate the diagnosis of this condition. Am. J. Med. Genet. 70:349–352, 1997.**



**KEY WORDS: craniosynostosis; short limbs; hair abnormalities; dental abnormalities; seizures; hypocalcemia**

## INTRODUCTION

Cranioectodermal dysplasia, also known as Sensenbrenner syndrome (MIM *218330) is an autosomal recessive condition characterized by craniofacial anomalies and skeletal and ectodermal dysplasia. According to the 1984 Freire-Maia and Pinheiro [1984] clinical classification of ectodermal dysplasias, CED is classified in group A, subgroup 1-2-3. In CED, ectoderm anomalies includes sparse, slow-growing, fine and hypopigmented hair, widely spaced teeth, hypodontia, microdontia, taurodontia, dental fusion, and/or enamel dysplasia. Craniofacial malformations and skeletal anomalies include dolichocephaly, sagittal synostosis, frontal bossing, epicanthal folds, anteverted nares, everted lower lip, short and narrow thorax, pectus excavatum, rhizomelia, symmetric brachydactyly, single palmar crease, variable clinodactyly, and syndactyly of the 2nd and 3rd fingers and/or toes. Osteopenia, convex vertebral bodies and delayed ossification may also be present.

Visceral anomalies include heart defects and hepatosplenomegaly and are the most inconsistent phenotypic manifestations.

## MATERIALS AND METHODS

### Clinical Report

The reported patient is a 27-month-old Caucasian girl born to non-consanguineous parents, a 21-year-old gravida 3 para 2-0-0-2 mother, and a 24-year-old father.

Apart from intrauterine growth retardation, the pregnancy was uneventful. The delivery was by spontaneous vertex at term. Birthweight was 1,899 g (3 standard deviation (SD) below the mean), length was 39.4 cm (4 SD below the mean), and head circumference (OFC) was 30.5 cm (3 SD below the mean). Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. There were three umbilical vessels. Simian creases and symmetric short fingers and toes were noted. The chest appeared small and a protuberant abdomen was noted. "Dwarfism" was suspected.

During the first two weeks, the child failed to grow, with the length, weight, and OFC falling to 6 SD below the mean.

At age 5 months the anterior fontanelle was still open; intermittent rotatory nystagmus, alternating esotropia, and anteverted nostrils were noted. The palate was high and broad, and 4th and 5th finger clinodactyly was present.

At age 14 months the length, weight, and OFC were still 6 SD below the mean. Prominent forehead and mild dolichocephaly were noted. There were only two partially erupted, cone-shaped, lateral incisors. Skin

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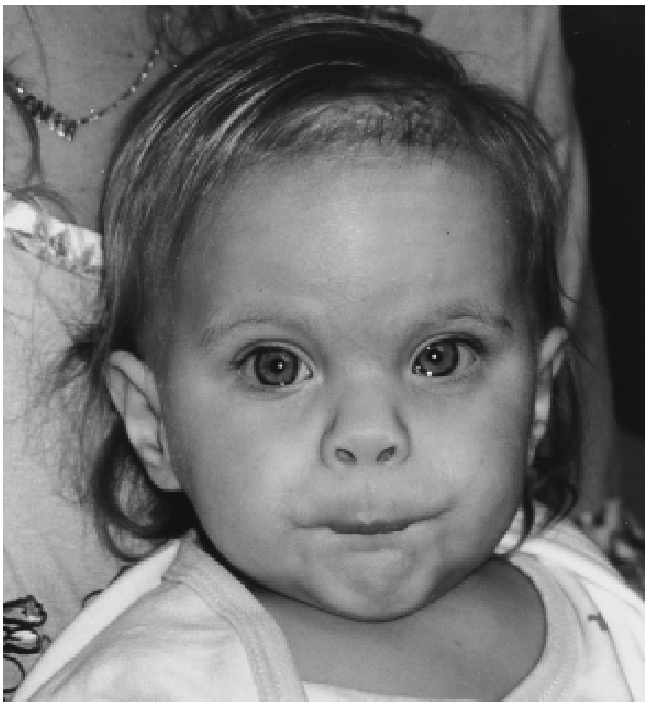

Figs. 1,2. Craniofacial features of the patient.

was dry, and there was periorbital hyperpigmentation. The scalp was hypotrichotic with hypopigmented, dry, and thin hair. Joint laxity and mild hypotonia were elicited. The mother reported photophobia. Psychomotor development was delayed; the child stood at 13 months and walked at age 19 months. At that time, her speech consisted of a few words. On the Bayley Scales of Infant Development her Mental Development Index was below 50 (3.35 standard deviations below the mean).

At 23 months the child was hospitalized after an episode of tetany. Serum calcium concentration was 5.5 mg/dl, ionized calcium 0.68 nmol/L, and her magnesium level was below 0.02 mg/dl. She responded to an IV dose of calcium.

At age 2 years, hoarse voice was noted. Frontal bossing, mild dolichocephaly, full cheeks, depressed nasal bridge, hypodontia, microdontia with delayed eruption, and dental diastema were present. There was also hypoplasia of the maxilla. Symmetric brachydactyly and mild cutaneous syndactyly of 2nd and 3rd toes were present (Figs. 1,2).

The mother is 165 cm tall and weighs 56 kg, the father is 185 cm tall and weighs 72 kg. Parental physical findings are normal. Sibs are healthy. Family history was unremarkable.

Figs. 3,4. X-rays of hands and feet at 18 months old, revealing no ossification centers at the radial heads; distal metacarpal, and metatarsal epiphyses; and proximal phalangeal epiphyses.

### Laboratory and Imaging Studies

Serum growth and thyroid hormones concentrations and chromosomes were normal. CT scan and MRI of the brain showed hypoplasia of the posterior corpus callosum leading to ventriculomegaly. At 17 months bone age was delayed, and no ossification centers were visible in hands, feet, hips and pelvis. There were periods of hypercalcemia alternated with periods of hypocalcemia (from 6.4 to 11.0 mg/dl), fluctuating serum PTH (from 27 to 55 PG/ml) and phosphorus concentrations (from 2.8 to 4.9 mg/dl). At 18 months, bone age was still markedly delayed, and no ossification centers were visible in the radial heads, distal metacarpal epiphyses and proximal phalangeal epiphyses (Figs. 3 and 4). At age 2, serum calcium and PTH concentrations were normal but vitamin D concentrations were low (12 PG/ml) (Figs. 5 and 6). Renal sonogram was normal.

### Differential Diagnosis

The differential diagnosis of CED includes disorders with dental abnormalities such as oligodontia, delayed eruption, abnormal shape, enamel abnormalities such as tricho-dento-osseous syndrome (TDO, MIM *190320), and chondroectodermal dysplasia (Ellis-Van Creveld syndrome, MIM *225500).

The skeletal findings of CED require a differentiation from conditions such as growth retardation-alopecia-pseudoanodontia-optic atrophy syndrome (GAPO syndrome, MIM *230740), metaphyseal dysplasia syndrome (cartilage-hair hypoplasia syndrome, MIM *250250), and pseudoachondroplastic dysplasia (MIM *264150).

## RESULTS

Manifestations such as dolichocephaly, frontal bossing, rhizomelia, characteristic hair and teeth abnormalities, as well as short thorax are consistent features and characterize CED (Table I). Other features are less common. Recurrent lung infections and relative hepatosplenomegaly were noted in some of the patients.

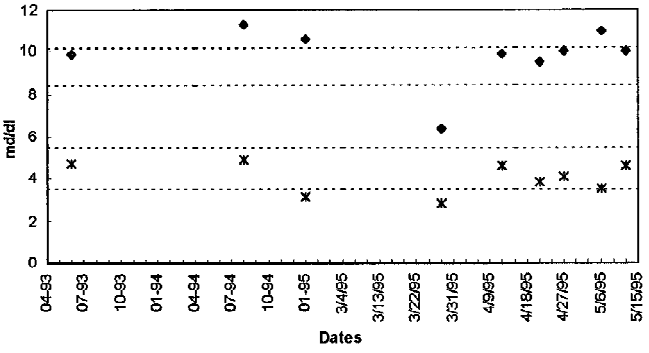


Fig. 5. Serum concentrations of calcium and phosphorous. ♦ = serum concentration of calcium. x = serum concentration of phosphorous. Dotted lines represent the upper and lower normal levels.

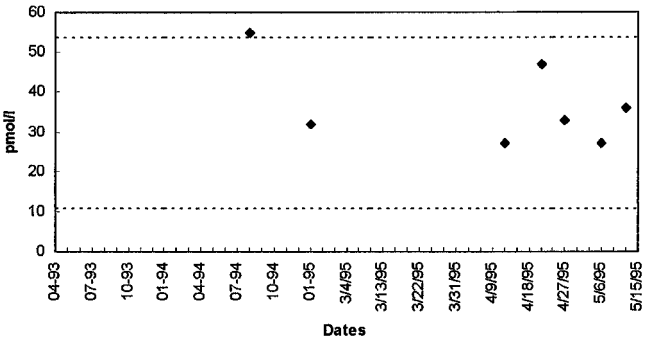


Fig. 6. Serum concentrations of PTH. ♦ = serum concentrations of PTH on several occasions. Dotted lines represent the upper and lower normal levels.

CNS anomalies other than hypoplastic corpus callosum have also been reported. Microcephaly and photophobia have not been previously described.

Another observation in the presented patient was the abnormal regulation of the parathyroid-bone axis. Such anomaly of homeostasis may induce electrolyte imbalance and lead to seizures or heart failure. This observation may have a bearing on the skeletal anomalies of this condition; abnormal feedback mechanism, deficiency of bone receptor(s), or inadequate PTH utilization in bones may account for the dysregulation. Such suppositions are corroborated by the two patients reported by Sensenbrenner et al. [1975], who also showed hypercalcemia.

## CONCLUSIONS

CED is a rare autosomal recessive condition. Because of the presence of "typical" CED features in several more frequent conditions, the CED diagnosis may be delayed.

The present report adds to the known CED manifestations, a new finding that could be life threatening. The abnormal regulation of the parathyroid-bone axis requires close monitoring and prompt, effective correction. Therefore early diagnosis of the condition is important.

Some of the CED characteristics are present during the prenatal period. Second and third trimester sonograms may show delayed and/or disproportionate biparietal-limbs measurements. Dwarfism may be suspected at birth. Later, the delayed developmental milestones and the ectodermal dysplasia may lead to inaccurate diagnosis. Head, hands, and spine x-rays are useful to the diagnosis of the condition (Table I).

A dozen patients have been reported. Bone anomalies included abnormal vertebral bodies and craniosynostosis, indirectly showing the underlying metabolic anomaly. Therefore, electrolyte monitoring is in order for the diagnosis and management of CED.

Thus, this report may contribute to the early diagnosis of CED, to the prevention of complications and to the better understanding of its pathogenesis.

TABLE I. Clinical Manifestations of Cranioectodermal Dysplasia*

| | Reference number | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 | | 5 | | | | | 7 | 4 | | U | P | |
| | Brothers | | Brothers | | MZ. twins | | | | Brothers | | | | |
| Features | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | % |
| Dolichocephaly | + | + | + | + | + | + | + | + | + | + | + | + | 100 |
| Frontal bossing | + | + | + | + | + | + | + | + | + | | − | + | 91 |
| Macrocephaly | − | − | − | − | − | − | − | − | + | − | − | − | 8 |
| Sagittal suture synostosis | + | − | + | − | + | − | + | − | + | − | + | − | 50 |
| Sparse, slow-growing, fine hair | + | − | + | + | + | + | + | + | + | − | + | + | 83 |
| Downslant fissures | + | + | − | − | − | − | − | − | − | − | − | − | 16 |
| Full cheeks | + | + | + | + | − | − | − | + | − | − | − | + | 50 |
| Epicanthal folds | + | + | + | + | + | + | + | − | − | + | − | − | 66 |
| Hypertelorism | + | − | − | − | − | − | − | − | − | − | − | +− | 8 |
| Hypotelorism | − | − | + | +− | +− | ? | +− | − | − | − | − | − | 8 |
| Hyperopia/myopia | − | − | + | + | − | − | − | − | + | − | − | − | 25 |
| Nystagmus | − | − | − | − | + | + | − | − | − | − | − | + | 25 |
| High palate | + | + | − | − | − | − | − | − | − | − | − | + | 25 |
| Dental abnormalities | + | + | + | + | + | + | + | − | + | + | + | + | 91 |
| Anteverted nares | − | − | + | + | + | + | − | − | − | − | − | + | 41 |
| Everted lower lip | + | + | + | + | + | + | − | − | − | − | − | + | 58 |
| Brachydactyly | + | + | + | + | + | + | + | + | − | − | + | + | 83 |
| Clinodactyly | − | − | + | − | + | + | − | + | − | − | − | − | 33 |
| Syndactyly 2nd–3rd toes | − | − | − | − | + | + | + | − | − | − | − | + | 33 |
| Rhizomelia | + | + | + | + | + | + | + | + | + | + | + | + | 100 |
| Single palmar crease | + | + | − | + | − | − | − | − | − | − | + | + | 41 |
| Pes equinovalgus | + | + | + | − | − | − | − | − | − | − | − | − | 25 |
| Osteoporosis | + | + | − | − | − | − | − | − | − | − | − | − | 16 |
| Short/narrow thorax | + | + | + | + | + | + | + | + | + | + | + | − | 91 |
| Pectus excavatum | + | + | + | + | + | + | − | + | − | − | − | − | 58 |
| Recurrent lung infections | − | + | − | + | − | − | − | − | + | + | + | + | 50 |
| Cardiac anomaly | − | + | − | + | − | − | − | − | − | − | − | − | 16 |
| Hepato/splenomegaly | + | + | − | − | − | − | − | − | − | − | + | + | 33 |
| Hypotonia | + | + | − | + | − | − | − | − | − | − | − | + | 33 |
| Joint laxity | − | − | − | − | + | + | + | − | − | − | − | + | 33 |
| Height below the 3rd centile | + | + | + | + | + | + | − | + | − | − | − | + | 66 |
| CNS anomaly | − | − | − | + | − | − | − | + | − | − | − | + | 25 |

*Clinical features and its prevalence in 10 reported, one unreported (U), and the present (P) patient.

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